A4 Sub B1

21. (Amended) The method of treating solid tumors of claim 17, wherein said liposomal topotecan formulation has a drug:lipid ratio by weight of about 0.05 to about 0.2.

A5 Sub B1

23. (Amended) A liposomal camptothecin unit dosage form, said unit dosage form comprising a lipid, a camptothecin dosage of from about 0.015 mg/M^2/dose to about 1 mg/M^2/dose and having a drug:lipid ratio by weight of about 0.05 to about 0.2

REMARKS

After entry of this amendment, claims 1-2 and 4-23 are pending in the above-identified application and are presented for examination. Claims 3 and 24-25 have been canceled without prejudice or disclaimer. Claims 1-2, 10-11, 16, 21 and 23-24 have been amended. The pending claims are set forth in the appendix for the Examiner's convenience.

Attached is a marked up version of the changes made to the specification and claims by the current amendment. That attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE". Reconsideration is respectfully requested.

I. THE INVENTION

The present invention provides improved liposomal topotecan unit dosage forms having surprisingly increased clinical efficacy and decreased collateral toxicity. In addition, the present invention provides methods of using such liposomal camptothecin compositions to treat neoplasia and to inhibit angiogenesis.

II. FORMAL MATTERS

The disclosure was objected to as allegedly page 1, line 5, did not state a U.S. patent application number. Applicants have amended the specification to clarify

that the proper U.S. Patent Application No. is 09/896,812. Entry of the amendment is respectfully requested.

With respect to the filing date of U.S. Patent Application No. 60/264,616, Applicants submit herewith a copy of the filing receipt, which evidences a filing date of January 26, 2001.

Claim 1 was amended to incorporate the features of original claim 3.

Claims 1-2, 10-11, 16, 21 and 23-24 were objected to because of the use of parentheses in the claims. Applicants have amended the claims to delete the use of parentheses. These changes are merely cosmetic in nature and do not effect the scope of the claims. No new matter has been added with the foregoing amendments. Accordingly, Applicants respectfully request that they be entered, and the objections be withdrawn.

III. OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION

Claims 1-11 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being obvious over claims 32-35, 37, 39-57, and 60-63 of co-pending Application No. 09/896,812. In the Office Action the Examiner has indicated that the double patenting rejections can be overcome by the filing of a Terminal Disclaimer (*see*, pages 2-3 of the Office Action mailed July 22, 2002).

Applicants respectfully request that the obviousness-type double patenting rejections be held in abeyance until Applicants receive from the Examiner an indication regarding allowable subject matter. At that time, Applicants will take the necessary steps to obviate any remaining double patenting rejection.

IV. REJECTION UNDER 35 U.S.C. § 101

Claims 24-25 have been rejected under 35 U.S.C. § 101 as allegedly being improper use claims. Applicants have canceled these claims without prejudice, rendering

this rejection moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.

V. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 9, 12 and 24-25 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. According to the Office Action, the phrase "trace amounts or greater" in claims 9 and 12 is indefinite.

The Examiner is respectfully reminded that the controlling case law on the construction of the second paragraph of §112 is set forth in *In re Borkowski,* 164 USPQ 642 (CCPA 1970). More particularly, in *In re Borkowski,* the court stated:

> The first sentence of the second paragraph of § 112 is essentially a requirement for *precision and definiteness* of claim language. If the scope of subject matter embraced by a claim is clear, and if the applicant has not otherwise indicated that he intends that claim to be of a different scope, then the claim does particularly point out and distinctly claim the subject matter which the applicant regards as his invention.

See, In re Borkowski, 44 F.2d 904, 164 USPQ 642, 645 (CCPA 1970).

It is clear from the above-quoted language of *In re Borkowski* that the second paragraph of §112 contains two requirements: (1) the first requirement calls for precision and definiteness; and (2) the second requirement is that the claims must be directed to the subject matter Applicant regards as his invention. The second requirement is not currently at issue because the claims cover what Applicants regard as their invention and no more. Thus, only the first requirement will be addressed.

With respect to the first requirement, one skilled in the art must be able to tell with a reasonable degree of certainty whether his or her activity is within or outside the scope of the claim. Simply stated, the claims must not be vague or indefinite and must set forth the boundaries of the subject matter for which protection is granted by the patent.

With regard to the phrase, "trace amounts or greater," Applicants assert that the phrase is indeed definite. One skilled in the art would be able to tell with certainty whether his or her activity is within or outside the scope of the claim.

In this regard, the Examiner's attention is respectfully directed to the dictionary definition of "trace amounts", which states, *inter alia,* an extremely small amount. Given this guidance, a person skilled in the art would be able to tell with certainty whether his or her activities are within the boundary for which protection is sought. The statute requires no more.

Moreover, as the Examiner is well aware, the phrase "trace amounts" is a well-known art recognized term. A person skilled in the art would immediately realize the definition meaning an extremely small amount, which may not be detectable using standard assay techniques. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the rejection.

The Office Action alleges that claims 24 and 25 are indefinite because they do not set forth any steps involved in the method/process. Applicants have canceled these claims without prejudice, rendering this rejection moot. Accordingly, Applicants respectfully request that this rejection be withdrawn.

VI. REJECTION UNDER 35 U.S.C. § 103(a)

Claims 1-25 have been rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,355,268 ("Slater *et al.*"), and further in view of PCT Publication No. WO 99/13816 ("Nexstar"). According to the Office Action, Slater *et al.* disclose liposome-entrapped topoisomerase inhibitors including camptothecin and camptothecin analogs such as topotecan and irinotecan. The Office Action acknowledges that the reference is silent with respect to the specific dosage as claimed in claims 1, 5, 17 and 22-23 and alleges that differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. According to the Office Action, it would have been obvious to

one of ordinary skill in the art to find the effective amounts set forth in the claims. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The present invention provides improved liposomal topotecan unit dosage forms having surprisingly increased clinical efficacy and decreased collateral toxicity. Claim 1 has been amended to clarify that the lipid comprises a mixture of sphingomyelin and cholesterol. Amended claim 1 sets forth the following:

> 1. (Amended) A liposomal topotecan unit dosage form, said unit dosage form comprising:
> a lipid; and
> a topotecan dosage of from about 0.01 mg/M^2/dose to about 7.5 mg/M^2/dose, wherein said liposomal topotecan unit dosage form has a drug:lipid ratio by weight of about 0.05 to about 0.2 and wherein said lipid comprises a mixture of sphingomyelin and cholesterol.

Claim 1 sets forth a liposomal topotecan unit dosage form of the specified dosage range (*i.e.*, about 0.01 mg/M^2/dose to about 7.5 mg/M^2/dose) comprising a lipid comprising sphingomyelin and cholesterol. Within this range, the claimed formulation is surprisingly efficacious, as seen from results in the examples in the specification (*see*, Figure 5 of the specification). Moreover, the data shown in the specification indicates that the claimed dosage form has surprisingly excellent efficacy at lower doses (*see*, page 20, lines 28-32 and Figure 5 of the specification). The dosage range claimed in the present invention is 0.01 mg/M^2/dose to about 7.5 mg/M^2/dose with a drug: lipid ratio of 0.05 to about 0.2. The data shown in the specification indicates that the claimed dosage form has surprisingly excellent efficacy at lower doses (*see*, page 20, lines 28-32 and Figure 5 of the specification). Thus, the present invention teaches a specific dosage range in the claimed formulation is surprisingly efficacious while showing decreased toxicity.

Slater *et al.* teach a composition for treating a tumor comprising a liposome and a topoisomerase inhibitor wherein the entrapped inhibitor is of at least

about 0.10 μmole drug per μmole lipid. Slater *et al.* do ***not*** teach the advantages of a liposome comprised of sphingomyelin and cholesterol. A description of these types of liposomes or sphingosomes are set forth in detail on page 7, paragraph 25, of the present application. Slater *et al.* show poor efficacy for low dosage of liposomal topotecan. For example, at 2 mg/kg liposomal topotecan dosage, most mice showed no response (*see*, Table 6, column 17 of Slater *et al.*). Table 6 is reproduced below for the Examiner's convenience.

TABLE 6

Treatment	Dose mg/kg	Complete Remission	Partial Remission	Non-Responsive
Saline		0	0	12
liposome-entrapped MPE-camptothecin	4	8	4	0
free topotecan	25	0	1	11
liposome-entrapped topotecan	2	1	2	9
liposome-entrapped topotecan	5	2	8	2
liposome-entrapped topotecan	8	7	3	2

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the cited art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Based on the results disclosed by Slater *et al.*, a skilled artisan would ***not*** have been motivated to use a ***lower*** dosage level of topotecan as is claimed by the present invention, because Slater *et al.* teach that such a low dose would not be expected to be

effective. Proceeding against conventional wisdom is strong evidence of nonobviousness (*see*, MPEP § 2145)

> The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F.2d 1038, 228 USPQ 685. (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyl sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).

A key point of difference between the present invention and Slater *et al.* are the efficacy levels seen at the lower dosage levels. The compositions of Slater *et al.* have poor efficacy at lower dosage levels compared to the dosage forms of the present invention, which are surprisingly efficacious. Therefore, the present invention is ***not*** obvious in view of Slater *et al.*

Nextstar does not supply the deficiencies of the primary reference. According to the Office Action, Nexstar discloses liposomal camptothecin formulations having improved pharmacokinetics, enhanced efficacy as anti-tumor agents. However, Nexstar does ***not*** teach or suggest a topotecan dosage of from about 0.01 mg/M^2/dose to about 7.5 mg/M^2/dose, wherein the liposomal topotecan unit dosage form has a drug:lipid ratio by weight of about 0.05 to about 0.2 and wherein said lipid comprises a mixture of sphingomyelin and cholesterol. As such, Applicants respectfully request that the rejection be withdrawn.

VII. OBJECTIVE EVIDENCE REBUTS ANY *PRIMA FACIE* CASE OF OBVIOUSNESS

Applicants can rebut a *prima facie* case of obviousness by presenting test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillion*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990).

Applicants maintain that a *prima facie* case of obviousness has not been established. However, data filed with the application rebuts any *prima facie* case of obviousness.

In this regard, the Examiner's attention is respectfully directed to Figures 3-A and 3-B. As illustrated therein, administration of free topotecan as a single intravenous dose had minimal effect on survival in the L1210 model (*see*, Figure 3A). At the highest dose of free topotecan, a median survival of 13 days (44% ILS) was observed. There was one long-term survivor (day 60) in this group.

In contrast, a single i.v. administration of liposomal topotecan at either 5 or 10 mg/kg resulted in 100% survival at day 60 (*see*, Figure 3B). Median survival for a 1 mg/kg dose was 13 days (44% ILS) and the survival curve was nearly identical to that of the free topotecan administered at 30 mg/kg – a 30-fold improvement in potency.

In addition to the foregoing free drug comparison, these results compare favorably with the data presented in Slater *et al.*, (Table 6, column 17), wherein a significant amount of the animals were non-responsive at this concentration of drug in liposomal form.

Further, the specification is replete with advantages of the present invention. For example, on page 10, lines 20-25, the specification sets forth:

> A recommended dose for **free topotecan** in Small Cell Lung Cancer is **1.5 mg/M^2 per dose**, every day for 5 days, repeated every three weeks. Because of the improvements in treatment now demonstrated in the examples, below, doses of topotecan in **liposomal topotecan** in humans will be effective at ranges as low as from **0.015 mg/M^2/dose**

> and will still be tolerable at doses as high as 15 to 75 mg/M^2/dose, depending on dose scheduling.

Because of these lower doses, there is a concomitant decrease in toxicity. In addition, on page 13, line 30, bridging to page 14, at the top, it states:

> At a 5 mg/kg dose of topotecan, a 164-fold increase in plasma AUC, a 24-fold increase in C_{max} and a 24-fold increase in the plasma α half-life were observed for the liposomal drug relative to the free drug (*see*, Table 1). Historically, large improvements in AUC and plasma half-lives of liposomal drugs have resulted in enhanced delivery of the drug to disease-sites (such as tumors), a process known as "disease-site targeting".

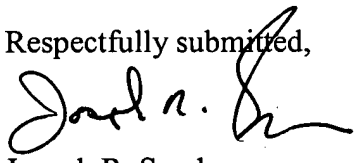
Thus, the liposomes of the present invention show better efficacy, reduced toxicity and function in disease-site targeting. It is apparent, therefore, that the liposomes of the present invention possess unexpected advantageous properties, not present in the prior art. This is objective evidence sufficient to rebut any *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection.

VIII. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

First paragraph on page 1 has been amended as follows:

The present application claims priority to U.S. Provisional Patent Application Nos. 60/215,556, filed June 30, 2000, and 60/264,616, filed January 26, 2001, both of which are hereby incorporated by reference in their entireties for all purposes. U.S. Patent Application No. 09/896,812, bearing Attorney Document No. 016303-008030, filed June 29, 2001, entitled "Liposomal Antineoplastic Drugs and Uses Thereof," is hereby incorporated by reference for all purposes.

In the claims:

Claims 3 and 24-25 have been cancelled.

Claims 1-2, 10-11, 16, 21 and 23-24 have been amended as follows:

1. (Amended) A liposomal topotecan unit dosage form, said unit dosage form comprising:

a lipid; and

a topotecan dosage of from about 0.01 mg/M^2/dose to about 7.5 mg/M^2/dose, wherein said liposomal topotecan unit dosage form has a drug:lipid ratio [(]by weight[)] of about 0.05 to about 0.2 and wherein said lipid comprises a mixture of sphingomyelin and cholesterol.

2. (Amended) The liposomal topotecan unit dosage form of claim 1, wherein said drug:lipid ratio [(]by weight[)] is about 0.05 to about 0.15.

10. (Amended) The liposomal topotecan formulation of claim 8, comprising a drug:lipid ratio [(]by weight[)] of about 0.05 to about 0.2.

11. (Amended) The liposomal topotecan formulation of claim 10, wherein said drug:lipid ratio [(]by weight[)] is about 0.05 to about 0.15.

16. (Amended) A method of treating solid tumors in a mammal, said method comprising:

administering to said mammal having a solid tumor of the lung, mammary and/or colon a liposomal topotecan formulation having a drug:lipid ratio [(]by weight[)] of about 0.05 to about 0.2.

21. (Amended) The method of treating solid tumors of claim 17, wherein said liposomal topotecan formulation has a drug:lipid ratio [(]by weight[)] of about 0.05 to about 0.2.

23. (Amended) A liposomal camptothecin unit dosage form, said unit dosage form comprising a lipid, a camptothecin dosage of from about 0.015 mg/M^2/dose to about 1 mg/M^2/dose and having a drug:lipid ratio [(]by weight[)] of about 0.05 to about 0.2.